(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082825 A1

(51) International Patent Classification[7]: C07D 215/00, 239/00, 491/00, A61K 31/435, A61P 25/16

(21) International Application Number: PCT/FI03/00254

(22) International Filing Date: 3 April 2003 (03.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/369,323 3 April 2002 (03.04.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/082825 A1

(54) Title: USE OF AN ALFA2-ADRENORECEPTOR ANTAGONIST FOR CNS-RELATED DISEASES

(57) Abstract: The invention relates to a method for the treatment of symptoms of disorders and conditions with sensorimotor gating deficits with an alpha2-adrenoceptor antagonist, or its pharmaceutically acceptable ester or salt thereof, being selective for the alpha2C-adrenoceptor subtype.

USE OF AN ALFA2-ADRENORECEPTOR ANTAGONIST FOR CNS-RELATED DISEASES

FIELD OF THE INVENTION

The present invention relates to a method for the treatment of symptoms of disorders and conditions associated with sensorimotor gating deficits. More specifically, in such a method a therapeutically effective amount of an alpha2-adrenoceptor antagonist, or its pharmaceutically acceptable ester or salt thereof, selective for the alpha2C-adrenoceptor subtype is administered to a mammal in need of such treatment.

BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention and in particular cases to provide additional details respecting the practice are incorporated by reference.

The startle reflex is a short-latency response of the skeletal musculature elicited by a sudden auditory stimulus. Prepulse-inhibition (PPI) of the startle response refers to the reduction in the startle response caused by a low intensity non-startling stimulus (the prepulse) which is presented shortly before the startle stimulus. PPI can be used as an operational measure of sensorimotor gating and appears to be present in all mammals, including rats and humans (Swerdlow, N. R. et al., *The Archives of General Psychiatry* **51** (1994) 139-154). Sensorimotor gating i.e. PPI deficits are observed in subgroups of patients with certain neuropsychiatric disorders, such as schizophrenia, obsessive compulsive disorder, Tourette's syndrome, blepharospasm and other focal dystonias, temporal lobe epilepsy with psychosis, drug-induced psychosis (Braff, D. L. et al., *Psychopharmacology (Berl)* **156(2-3)** (2001) 234-258), and panic disorder (Ludewig, M.S. et al, *Depression and Anxiety* **15** (2002) 55-60). These PPI deficits can be produced in animals by psychostimulants, such as d-amphetamine or phencyclidine (PCP), and reversed by some antipsychotics. The PPI model has been shown to possess high predictive validity and it is therefore widely

used in the development of new therapeutic agents (Swerdlow, N. R. et al., *The Archives of General Psychiatry* **51** (1994) 139-154). Some, but not all, antipsychotics have also weak PPI-enhancing effects *per se*. The mechanisms how PPI is modulated in the CNS are complicated and only partially understood.

The alpha2-adrenoceptors, which include three subtypes (alpha2A, alpha2B, and alpha2C) encoded by three genes, mediate many of the central nervous system (CNS) effects of norepinephrine and regulate the release of several other neurotransmitters in addition to norepinephrine. The alpha2-adrenoceptors are suggested to have modulatory roles in various neuropsychiatric disorders, but their significance in the development of new therapeutics for CNS disorders, especially the role of each alpha2-receptor subtypes is poorly known due to the unavailability of selective ligands for each of the alpha2-adrenoceptor subtypes. However, some hypotheses about the significance of the alpha2-subtypes in CNS disorders has been gained by studies employing mice with genetically altered alpha2-subtype expression, which has produced new hypotheses about the possible actions of alpha2-subtype selective ligands (MacDonald. E. et al., *Trends Pharmacol. Sci.* **18** (1997) 211-219; Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85).

Subtype non-selective alpha2-adrenoceptor agonists are known to decrease startle reflex and antagonists to enhance startle reflex. However, the effects of alpha2-agonists or antagonists on the sensorimotor gating phenomenon (i.e. on the prepulse inhibition of startle reflex) are unclear; the general conclusion is that PPI is not altered, but the interpretation is confounded by the effects of alpha2-drugs on startle *per se* (Geyer, M. A. et al., *Psychopharmacology (Berl)* **156(2-3)** (2001) 117-154).

SUMMARY OF THE INVENTION

The object of the present invention is to provide a new treatment possibility for symptoms of diseases and conditions characterized by sensorimotor gating deficits. The invention describes how a subtype selective alpha2C-adrenoceptor antagonist, but not subtype non-selective alpha2-adrenoceptor antagonist, enhances sensorimotor gating (i.e. the prepulse-inhibition of startle reflex) *per se* and

especially when the normally functioning sensorimotor gating is disrupted by the psychostimulant phencyclidine (PCP).

Additional objects and advantages of the invention will be set forth in part in the description, which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B show the effect of the selective alpha2C-antagonist acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenyl]amine (JP-1302) (WO 01/64645) on the startle reflex and its prepulse inhibition in rats. The selective alpha2C-antagonist enhanced sensorimotor gating (prepulse inhibition %) without significantly affecting the startle reactivity to intense pulses without prepulses. Asterisk refers to significant difference between vehicle and treatment group $p<0.05$; 1-way ANOVA and LSD post hoc test.

Figures 2A and 2B show the effect of the alpha2C-antagonist acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenyl]amine (JP-1302) and the alpha2-adrenoceptor subtype non-selective alpha2-antagonist atipamezole on the startle reflex and its prepulse inhibition in rats pretreated with the psychostimulant phencyclidine (PCP). PCP clearly disrupted the PPI and this was effectively counteracted by the subtype selective alpha2C-antagonist, but not by the receptor subtype non-selective alpha2-antagonist atipamezole. Asterisks refer to significant difference in statistical comparisons between the vehicle (veh) + PCP and other treatment groups. * $p <$ 0.05, ** $p < 0.01$, *** $p < 0.001$; 1-way ANOVA and LSD post hoc test.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel therapeutic approach to treat the symptoms of disorders and conditions associated with sensorimotor gating deficits in mammals, including humans and animals. The results to be presented below show that a subtype selective alpha2C-adrenoceptor antagonist, but not subtype non-selective alpha2-adrenoceptor antagonist, enhances sensorimotor gating (i.e. the prepulse-inhibition of startle reflex) *per se*.

In a previous study (Sallinen, J. et al., *J. Neurosci.* **18** (1998) 3035-42), alpha2C-knockout mutation was associated with weakened PPI whereas alpha2C-overexpression demonstrated increased PPI. It was therefore speculated, that alpha2C-subtype-selective drugs might have therapeutic value in disorders associated with sensorimotor gating deficits. The novel selective alpha2C-antagonist acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenyl]amine (JP-1302) has now been tested for its therapeutic value in disorders associated with sensorimotor gating deficits. The results obtained with alpha2C-antagonist turned out to be unexpected, since the previous studies with transgenic mice suggested that an alpha2C-agonist (but not antagonist) would enhance PPI (since overexpression of alpha2C enhanced PPI). Also the magnitude of the effect of the alpha2C-antagonist acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenyl]amine (JP-1302) can be considered surprising, and the observed effect could not have been anticipated on theoretical basis (genetically altered alpha2C-expression did not affect the PCP –disrupted PPI, Sallinen, J. et al., *J. Neurosci.* **18** (1998) 3035-42).

In order to study the effect of alpha2-antagonists on startle reflex and its prepulse – inhibition, groups of rats (n =10/group) were pre-treated with the alpha2C-antagonist or vehicle 20 min before measurement of the acoustic startle reactivity and PPI in a test system designed for startle studies (SR-LAB, San Diego Instruments, CA, USA). In a subsequent experiment the effects of the alpha2-adrenoceptor subtype selective alpha2C-antagonist and or the subtype non-selective antagonist atipamezole (Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582) on PCP-induced PPI –disruption was studied. The antagonists were given 20 min, and PCP or vehicle 10 min before start of the startle measurements. The method

otherwise corresponds to the procedure described in Sallinen, J. et al., *J. Neurosci.* **18** (1998) 3035-42.

It was found that the receptor subtype selective alpha2C-antagonist acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenyl]amine (JP-1302) did not affect the startle reflex *per se*, but it increased PPI dose-dependently and effectively (Figures 1A and 1B). The effect of the alpha2C-antagonist was especially clearly seen in the presence of PCP (Figures 2A and 2B). In the Figures 2A and 2B it is also shown that the specific and potent alpha2-antagonist atipamezole, that has no alpha2-adrenoceptor subtype selectivity, increased significantly the startle reactivity *per se*, but it had no effect on the PPI phenomenon; this points to the significance of the alpha2C-adrenoceptor subtype selective antagonism.

The present findings suggest that an alpha2C-adrenoceptor selective antagonist can be used to treat symptoms of disorders and conditions associated with sensorimotor gating deficit, particularly symptoms of disorders and conditions wherein the sensorimotor gating deficits results in sensory flooding and cognitive fragmentation causing dysfunction in attention and perception. Such disorders and conditions include, but are not limited to, schizophrenia, obsessive compulsive disorder, Tourette's syndrome, blepharospasm and other focal dystonias, temporal lobe epilepsy with psychosis, drug-induced psychosis (for example, psychosis caused by chronic use of dopaminergic agents), Huntington's disease, Parkinson's disease, disorders caused by fluctuation of the levels of sex hormones (such as premenstrual syndrome), and panic disorder.

Further, said symptoms, which are usually associated with above-mentioned disorders or conditions include, but are not limited to, hallucination, delusion, parathymia, agitation, psychotic cognitive impairment (including deficits in thinking and speech), social withdrawal and withdrawal symptoms (including delirium) associated with cessation of cigarette smoking or alcohol or drug abuse.

These symptoms may also be seen in animals in exceptional circumstances, for example, during withdrawal from masters or during transportation.

Furthermore, the present invention relates the use of an alfa2-adrenoceptor antagonist, or its pharmaceutically acceptable ester or salt thereof, said alfa2-

adrenoceptor antagonist being selective for the alfa2C-adrenoceptor subtype, in the manufacture of a pharmaceutical for the treatment of symptoms of disorders and conditions associated with sensorimotor gating deficits in a mammal.

For the purposes of the invention the term "treatment" means treatment in order to remedy or alleviate the symptoms of the disorder or condition, and treatment in order to prevent the development or the exacerbation of the symptoms.

For the purposes of the invention the term "alpha2C-selective antagonist" or "an alpha2-adrenoceptor antagonist selective for the alpha2C-adrenoceptor subtype" refers to a compound having no other major affinities for other alpha2-adrenoceptor subtypes than for alpha2C-adrenoceptor subtype. Accordingly, the alpha2-adrenoceptor antagonist should be at least ten-fold more selective for the alpha2C-adrenoceptor subtype than for other alpha2-adrenoceptor subtypes.

Furthermore, the use of an alpha2-adrenoceptor antagonist selective for the alpha2C-adrenoceptor subtype in combination with other psychiatric medication, that is used in conditions in which sensorimotor gating deficits may appear, would be therapeutically beneficial by providing either an effective treatment to patient resistant to the said conventional therapeutic agents alone, or by providing a synergistic action with the said conventional therapeutic agents. Such psychiatric medication include, but is not limited to, an anxiolytic, antidepressive or antipsychotic drug, which drug does not need to have effect on sensorimotor gating deficits.

The alpha2-adrenoceptor antagonist selective for the alpha2C-adrenoceptor subtype and the second compound should preferably be administered to the patient during the same period of treatment. The most preferably, the alpha2-adrenoceptor antagonist selective for the alpha2C-adrenoceptor subtype and the second compound should be administered simultaneously. According to a particularly preferable embodiment, these compounds are administered from the same dosage form.

Such a combination therapy will allow the use of smaller doses of the said compounds and thereby substantially reduce their possible sedative effects, their disturbance on motor functionality, and other adverse effects such as hypotensive effects.

For the purpose of the invention the alpha2-adrenoceptor antagonist; or its pharmaceutically acceptable ester or salt, selective for the alpha2C-adrenoceptor subtype can be administered by various routes. Typical routes of administration include, but are not limited to, oral, transdermal, transmucosal, and parenteral routes. One skilled in the art would recognize the dosage forms suitable in the method of the present invention.

The precise amount of the drug to be administered to a mammal according to the present invention is dependent on numerous factors known to one skilled in the art, such as the compound to be administered, the general condition of the patient, the condition to be treated, the desired duration of the treatment, the type of mammal, the method and route of administration etc. For a subtype selective alfa2C-antagonist the usual daily dosage will be from 1 to 500 mg, preferably from 10 to 30 mg, divided in 1 to 4 individual doses.

Those skilled in the art will appreciate that the embodiments described in this application could be modified without departing from the inventive concept. Those skilled in the art also understand that the invention is not limited to the particular disclosed embodiments, but is intended to also cover modifications to the embodiments that are within the spirit and scope of the invention.

CLAIMS

1. Use of an alfa2-adrenoceptor antagonist, or its pharmaceutically acceptable ester or salt thereof, said alfa2-adrenoceptor antagonist being selective for the alfa2C-adrenoceptor subtype, in the manufacture of a pharmaceutical for the treatment of symptoms of disorders and conditions associated with sensorimotor gating deficits.

2. The use according to claim 1, wherein the symptom is hallucination, delusion, parathymia, agitation, psychotic cognitive impairment, social withdrawal and/or withdrawal symptom associated with cessation of cigarette smoking or alcohol or drug abuse.

3. The use according to claim 1, wherein the symptom is hallucination.

4. The use according to claim 1, wherein the symptom is delusion.

5. The use according to claim 1, wherein the symptom is parathymia.

6. The use according to claim 1, wherein the symptom is agitation,

7. The use according to claim 1, wherein the symptom is psychotic cognitive impairment.

8. The use according to claim 1, wherein the symptom is social withdrawal.

9. The use according to any one of claims 1 to 8, wherein the disorder or condition is schizophrenia, obsessive compulsive disorder, Tourette's syndrome, blepharospasm and other focal dystonias, temporal lobe epilepsy with psychosis, drug-induced psychosis, Huntington's disease, Parkinson's disease, disorder caused by fluctuation of the levels of sex hormones or panic disorder.

10. The use according to any one of claims 1 to 8, wherein the disorder is schizophrenia.

11. The use according to any one of claims 1 to 8, wherein the disorder is obsessive compulsive disorder.

12. The use according to any one of claims 1 to 8, wherein the disorder is Tourette's syndrome.

13. The use according to any one of claims 1 to 12, wherein the administering of the alpha2-adrenoceptor antagonist selective for the alpha2C-adrenoceptor is combined with the administering of other psychiatric medication.

14. The use according to any one of claims 1 to13, wherein the mammal is a human.

15. The use according to any one of claims 1 to 8 or 13, wherein the mammal is an animal.

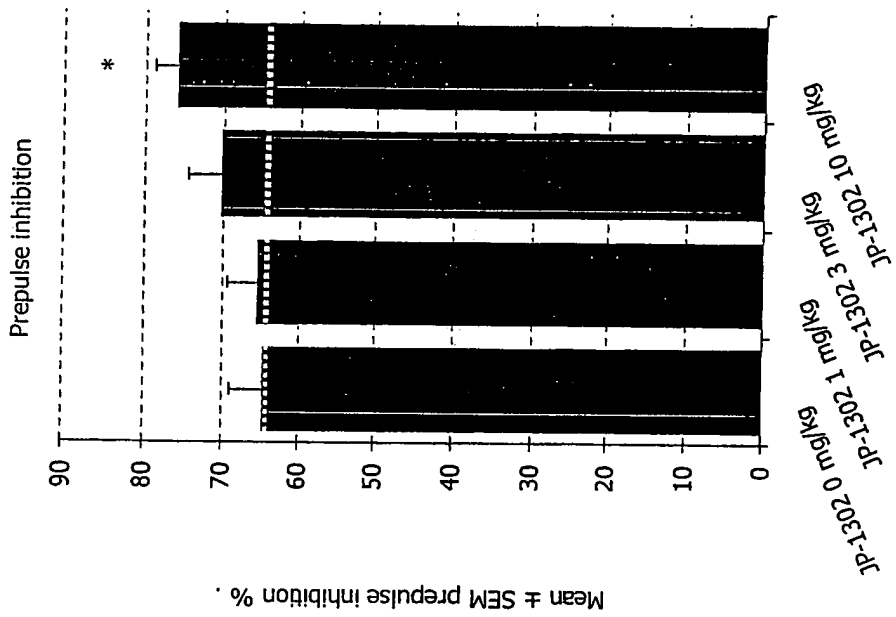

FIG. 1B

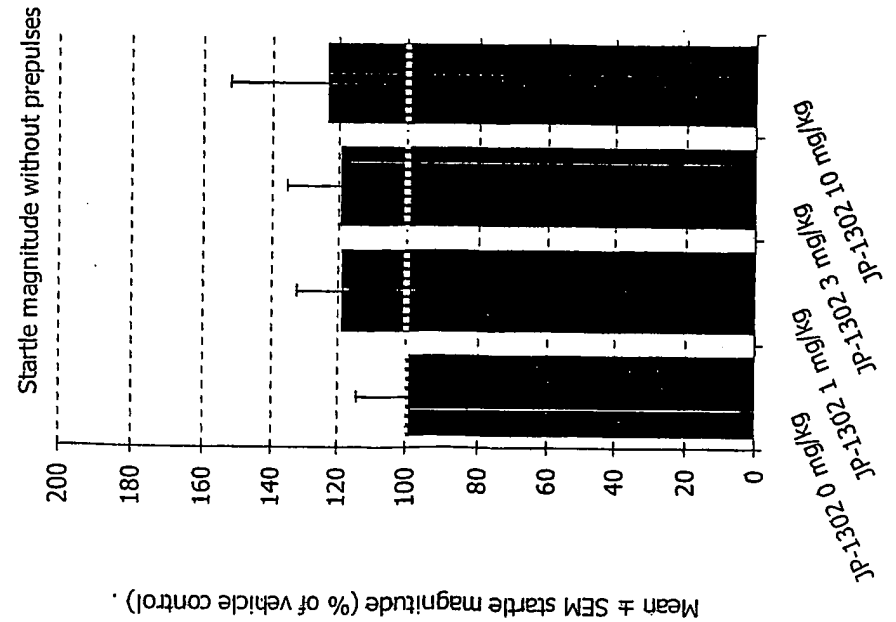

FIG. 1A

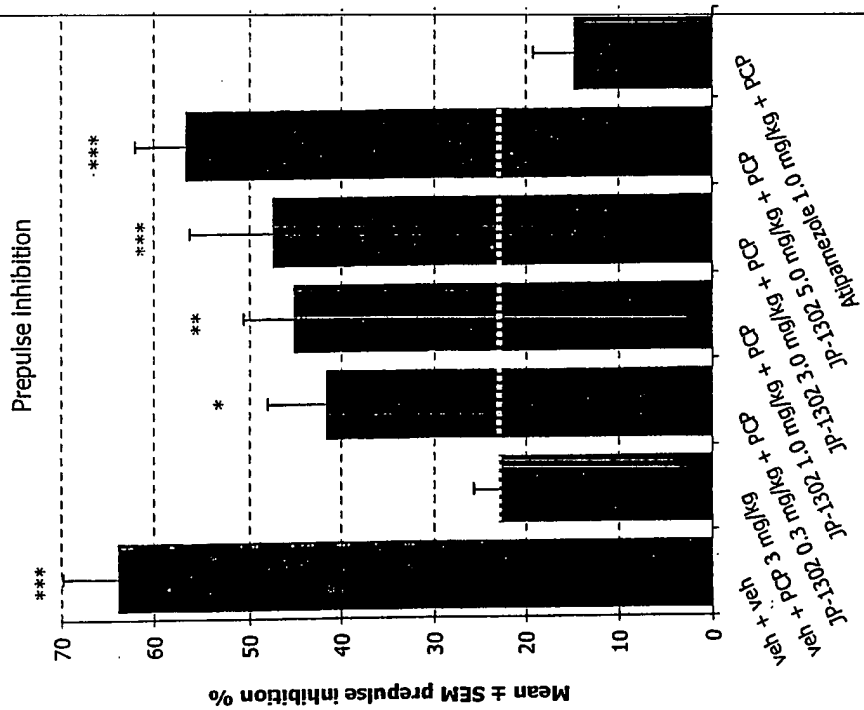

FIG. 2B

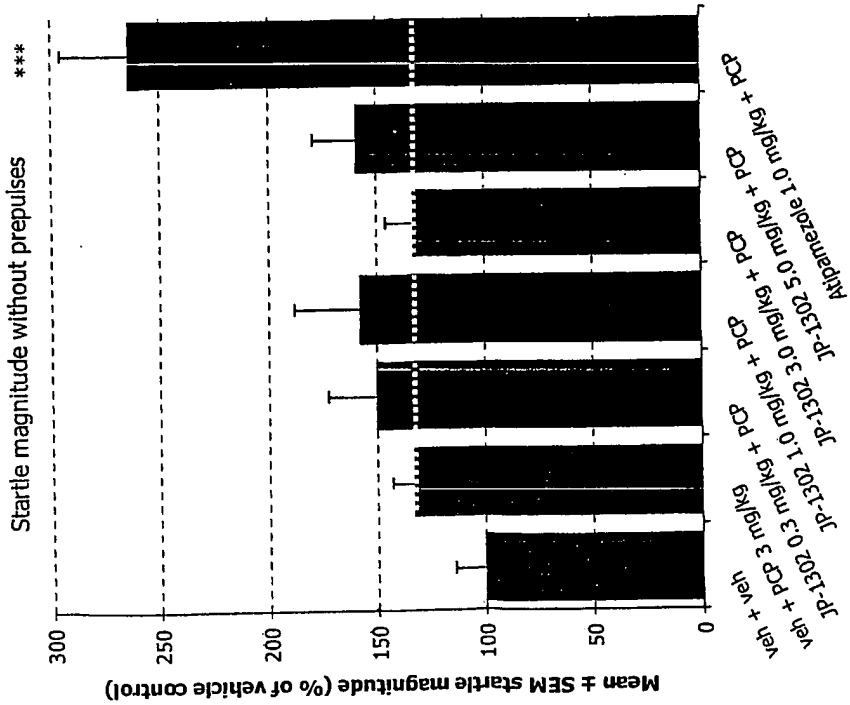

FIG. 2A

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/FI 03/00254

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/00 C07D239/00 C07D491/00 A61K31/435 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 64645 A (SAVOLA JUHA MATTI ;WURSTER SIEGFRIED (FI); ENGSTROEM MIA (FI); HOE) 7 September 2001 (2001-09-07) claim 11 ---	1-15
X	WO 02 18348 A (HOFFMANN LA ROCHE) 7 March 2002 (2002-03-07) page 3, line 13 - line 14 ---	1-15
X	US 4 604 398 A (WARD TERENCE J) 5 August 1986 (1986-08-05) column 2, line 55 ---	1-15
X	US 4 686 226 A (HUFF JOEL R ET AL) 11 August 1987 (1987-08-11) column 1, line 5 - line 60 ---	1-15
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	-7. 07. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	FERNANDO FARIETA / ELY

orm PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/FI 03/00254

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6 426 350 B1 (BISCHOFF FRANCOIS PAUL ET AL) 30 July 2002 (2002-07-30) column 1, line 5 - line 30 ---	1-15
X	US 6 352 999 B1 (BRAEKEN MIRIELLE ET AL) 5 March 2002 (2002-03-05) column 1, line 10 - line 30 ---	1-15
P,X	US 6 495 555 B1 (KENNIS LUDO EDMOND JOSEPHINE ET AL) 17 December 2002 (2002-12-17) column 1, line 10 - line 25 ---	1-15
X	WO 00 37466 A (JANSSEN PHARMACEUTICA NV ;KENNIS LUDO EDMOND JOSEPHINE (BE); MERTE) 29 June 2000 (2000-06-29) claim 6 ---	1-15
X	US 6 156 757 A (LOVE CHRISTOPHER JOHN ET AL) 5 December 2000 (2000-12-05) column 1, line 10 - line 20 ---	1-15
P,A	US 2002/045614 A1 (BECKER CYRUS KEPHRA ET AL) 18 April 2002 (2002-04-18) claims 1-32 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 03/00254

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15

The wording "sensorimotor gating deficits" is considered unclear and undefined in reference with the kind of diseases or symptoms such wording is limited to. Therefore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to:

The alpha 2C antagonist cited in the description (Page 4 lines 12-22) as JP-1302 and structurally related compounds with diseases or symptoms according to broad claims 1-15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/FI 03/00254

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